

# Figure 2: Clone 7.7 is the homolog of human clone **KIAA0313**

Clone 7.7 exhibits 75% identity and 95% similarity of human clone KIAA0313.

SSTTKGLIARKEGRYREPPPTPPGYV SSTTKGLIARKEGRYREPPPTPPGYI ***********	EAPAPGQTPP-AAAASRPGSKPQ SDTAGPSSVQQPHGHPTSSRPVNKPQ ::*. * **.	(SEQ ID NO: 28) (amino acid nos. 1348 to 1499 of SEQ ID NO: 2)
GGKDVSAEAESSSMVPVTTEEAKPVPMPAHIAVTPSTTKGLIARKEGRYREPPPTPPGYV GGKDVSIEAESSSLTSVTTEETKPVPMPAHIAVASSTTKGLIARKEGRYREPPTPPGYI	GIPIADFPEGPCHPARKPPDYNVALQRSRMVARPTEAPAPGQTPP-AAAASRPGSKPQ GIPITDFPEGHSHPARKPPDYNVALQRSRMVARSSDTAGPSSVQQPHGHPTSSRPVNKPQ ************************************	WHKPSDADPRLAPFQAGFAGAEEDEDEQVSAV WHKPNESDPRLAPYQSQGFSTEEDEDEQVSAV **** :: : * * * * * * * * * * * * * * *
Clone7.7 KIAA0313	Clone7.7 KIAA0313	Clone7.7 KIAA0313
2/34		



## 4618 b.p.

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31/11
  atg aaa tca cta gca atc cca gct aac cat gga gtt atg ggc cag cag gag aaa cac tca
  M K P L Ă I P A N H G V M G Q Q E K H S
  ctt cct gca gat ttc aca aaa ctg cat ctt act gac agt ctc cac cca cag gtg acc cac
  LPADFTKLHLTDSLHPQVTH
  121/41
  gtt tet tet age cat tea gga tgt agt ate aet agt gat tet ggg age age agt ett tet
  v s s š н s g ̃ c ́ s ́ i т s Ď s g ̃ s ́ s ́ s ̃ L ́ s
  gat atc tac cag gcc aca gaa agc gag gct ggt gat atg gac ctg agt ggg ttg cca gaa
  DIYQATESEAGDMDLSGLPE
  241/81
  aca gca gtg gat tcc gaa gac gac gac gat gaa gaa gac att gag aga gca tca gat cct
  T A V D S E D D D D E E D I E R A S D P
  301/101
                          331/111
  ctg atg agc agg gac att gtg aga gac tgc cta gag aag gac cca att gac egg aca gat
  LMSRDIVRDCLEKDPIDRTD
                          391/131
  gat gac att gaa caa ctc ttg gaa ttt atg cac cag ttg cct gct ttt gcc aat atg aca
  Ď Ď I Ĕ Q L L Ĕ F M H Q Ľ P <u>A F A N M Ť</u>
 atg tca gtg agg cga gaa ctc tgt gct gtg atg gtg ttc gca gtg gtg gaa aga gca ggg
 M S V R R E L C A V M V F A V V E R A G
                         511/171
 acc ata gtg tta aat gat ggt gaa gag ctg gac tcc tgg tca gtg att ctc aat gga tct
 TIVLNDGEELDSWSVILNGS
                         571/191
 gtg gaa gtg act tat cca gat gga aaa gca gaa ata ctg tgc atg gga aat agt ttt ggt
                                                                       cNMP-BD
 V E V T Y P D G K A E I L C M G N S F G
 601/201
 gte tet eet ace atg gae aaa gaa tae atg aaa gga gtg atg aga aca aag gtg gat gae
 V S P T M D K E Y M K G V M R T K V D D
 661/221
                         691/231
 tgc cag ttt gtc tgc ata gcc cag caa gat tac tgc cgt att ctc aat caa gta gaa aag
 <u>C O F V Č I A O O D Y C R I L N O V E K</u>
 721/241
                         751/251
 aac atg caa aaa gtt gaa gag gaa gga gag att gtt atg gtg aaa gaa cac cga gaa ctt
 <u>N M O K V E E E G E I V M</u> V K E H R E L
                         811/271
gat cga act gga aca aga aag gga cac att gtc atc aag ggt acc tca gaa agg tta aca
D R T G T R K G H I V I K G T S E R L T
 841/281
                         871/291
atg cat tig gig gaa gag cat ica gia gia gat cca aca tic ata gaa gac tit cig tig
                                                                           REM
MHLVEEHSVVDPTFIEDFLL
901/301
ace tat agg act tit cit tet age cea atg gaa gtg gge aaa aag tta ttg gag tgg tit T Y R T F L S S P M E V G K K L L E W F
                        991/331
aat gac ccg agc ctc agg gat aag gtt aca cgg gta gta tta ttg tgg gta aat aat cac
<u>N D</u> P S L R D K V T R V V L L W V N N H
ttc aat gac ttt gaa gga gat cct gca atg act cga ttt tta gaa gaa ttt gaa aac aat
FNDFEGDPAMTRFLEEFENN
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REPLACEMENT ShEET - Apply. 09/911,826 Filed July 20,2001



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1081/361
                          1111/371
   ctg gaa aga gag aaa atg ggt gga cac cta agg ctg ttg aat atc gcg tgt gct gct aaa
   LEREKMGGHLRLLNIACAAK
   1141/381
                          1171/391
  gca aaa aga aga ttg atg acg tta aca aaa cca tcc cga gaa gct cct ttg cct ttt atc
  Ă K R R L <u>M T L T K P S R E Ă P L P F I</u>
   1201/401
                          1231/411
  tta ett gga gge tet gag aag gga ttt gga ate ttt gtt gac agt gta gat tea ggt age
  L L G G S E K G F G I F V D S V D S G S
                          1291/431
  aaa gca act gaa gca ggc ttg aaa cgg ggg gat cag ata tta gaa gta aat ggc caa aac
    ATEAGLKRGDOILEVNGON
  1321/441
                          1351/451
  ttt gaa aac att cag ctg tca aaa gct atg gaa att ctt aga aat aac aca cat tta tct
  F E N I Q L S K A M E I L R N N T H L S
  1381/461
                         1411/471
  atc act gtg aaa acc aat tta ttt gta ttt aaa gaa ctt cta aca aga ttg tca gaa gag
  <u>ITVKTNLFVF</u>KELLTRLSEE
  1441/481
                         1471/491
  aaa aga aat ggt gcc ccc cac ctt cct aaa att ggt gac att aaa aag gcc agt cgc tac
 KRNGAPHLPKIGDIKKASRY
  1501/501
                         1531/511
 tcc att cca gat ctt gct gta gat gta gaa cag gtg ata gga ctt gaa aaa gtg aac aaa
 SIPDLAVDVEQVIGLEKVNK
  1561/521
                         1591/531
 aaa agt aaa gcc aac act gtg gga gga agg aac aag ctg aaa aag ata ctc gac aag act
 K S K Ă N T V Ğ Ğ Ř N K L K K I L D K T
                         1651/551
 egg ate agt ate ttg cea cag aaa eea tae aat gat att ggg att ggt eag tet caa gat
 RĬSĬĿPQĸPYNDĬGĬĞQŠQD
 1681/561
                         1711/571
 gac age ata gta gga tta agg cag aca aag cac ate cca act gca ttg cet gte agt gga
 DSIVGLRQTKHIPTALPVSG
 1741/581
                         1771/591
 ace tha tea ice agt aat cet gat tha tig eag tea cat eat ege att tha gae the agt
 T L S S N P D L L Q S H <u>H R I L D F S</u>
 1801/601
                         1831/611
 get act cet gae tig cea gat caa gig eta agg git tit aag get gat eag eaa age ege
 <u>A T P D L P D O V L R V F K A D O O S R</u>
                         1891/631
tac atc atg atc agt aag gac act aca gca aag gaa gtg gtc att cag gct atc agg gag
Y I M I S K D T T A K E V V I Q A I R E
 1921/641
                        1951/651
ttt get git act gee ace eeg gat eaa tat tea eta tgt gag gte tet gte aca eet gag
FAVTATPDOYSLCEVSVTPE
1981/661
                        2011/671
gga gta atc aaa caa aga aga ctt cca gat cag ctt tcc aaa ctt gca gac aga ata caa
<u>G V I K O R R L P D O L S K L A D R I O</u>
                        2071/691
ctg agt gga agg tat tat ctg aaa aac aac atg gaa aca gaa act ctt tgt tca gat gaa
<u>LSGRYYLKNNME</u>TETLCSDE
                       2131/711
gat get eag gag tig tig aga gag agt caa att tee ete ett eag ete age aet gig gaa
D A Q E L L R E S Q I <u>S L L Q L S T V E</u>
2161/721
                       2191/731
gtt gca aca cag ctc tct atg cga aat ttt gaa ctc ttt cgc aac att gaa cct act gaa
<u>V A T Q L S M R N F E L F R N I E P T E</u>
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PDZ

RA

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```
2221/741
                          2251/751
  tat ata gat gat tta ttt aaa ctc aga tca aaa acc agc tgt gcc aac ctg aag aga ttt
  YIDDLFKLRSKTSCANLKRF
  2281/761
  gaa gaa gtc att aac cag gaa aca ttt tgg gta gca tct gaa att ctc aga gaa aca aac
  <u>E E V I N O E T F W V A S E I L R E T N</u>
  2341/781
  cag ctg aag atg aag atc att aag cat ttc atc aag ata gca ctg cac tgt agg gaa
  <u>Q L K Ř M K I I K H F I K I A L H Č R Ě</u>
                          2431/811
                                                                         CDC25
 tgc aag aat ttt aac tca atg ttt gca atc atc agt ggc cta aac ctg gca cca gtg gca
 <u>C K N F N S M F A I I S G L N L A P V A</u>
 2461/821
                          2491/831
 aga ctg cga acg acc tgg gag aaa ctt ccc aat aaa tac gaa aaa cta ttt caa gat ctc
 <u>R L R T T W E K L P N K Y E K L F Q D L</u>
                         2551/851
 caa gac ctg ttt gat cct tcc aga aac atg gca aaa tat cgt aat gtt ctc aat agt caa
 <u>Q D L F D P S R N M A K Y R N V L N S Q</u>
                         2611/871
 aat cta caa cct ccc ata atc cct cta ttc cca gtt atc aaa aag gat ctc acc ttc ctt
 N L Q P P I I P L F P V I K K D L T F L
 2641/881
                         2671/891
 cac gaa gga aat gac tca aaa gta gac ggg ctg gtc aat ttt gag aag cta agg atg att
 H E G N D S K V D G L V N F E K L R M I
 2701/901
                         2731/911
 gca aaa gaa att cgt cac gtt ggc cga atg gct tca gtg aac atg gac cct gcc ctc atg
 A K E I R H V G R M A S V N M D P A L M
                         2791/931
 tte agg act egg aag aag aaa tgg egg agt ttg ggg tet ete age eag ggt agt aca aat
                                                                      Insertion
 FRTRKKKWRSLGSLSQGSTN
                                                                      Unique to
                         2851/951
                                                                      GRF4
 gca aca gtg cta gat gtt gct cag aca ggt ggt cat aaa aag cgg gta cgt cgt agt tcc
 ATVLDVÄQTGÖHKKRVRRSS
                         2911/971
ttt ctc aat gcc aaa aag ctt tat gaa gat gcc caa atg gct cga aaa gtg aag cag tac
F L N A K K L Y E Ď A Q M A R K V K Ŏ Ÿ
2941/981
                        2971/991
ctt tee aat tig gag eta gaa atg gae gag gag agt ett eag aca tia tet etg eag igt
L S N L E L E M D E E S L O T L S L O C
                                                            Continuation of the
3001/1001
                         3031/1011
                                                            CDC25 domain
gag cca gca acc aac aca ttg cct aag aat cct ggt gac aaa aag cct gtc aaa tcc gag
<u>Ĕ P A T N T</u> L P K N P G D K K P V K S E
3061/1021
                         3091/1031
acc tet eca gta get eca agg gea ggg tea eaa eag aaa get eag tee etg eea eag ece
T S P V Ă P R Ă G Š Q Q K Ă Q S L P Q P
                         3151/1051
cag cag cag cca cca cca gca cat aaa atc aac cag gga cta cag gtt ccc gcc gtg tcc
QQQPPPAHKINQGLQVPAVS
                        3211/1071
ctt tat cct tca cgg aag aaa gtg ccc gta aag gat ctc cca cct ttt ggc ata aac tct
LYPSRKKVPVKDLPPFGINS
3241/1081
                        3271/1091
cca caa gct tta aaa aaa att ctt tct ttg tct gaa gaa gga agt ttg gaa cgt cac aag
PQALKKILSLŠEEGŠLERHK
                        3331/1111
aaa cag get gaa gat aca ata tea aat gea tet teg eag ett tet tet eet eet aet tet
K Q Ă Ĕ Ď T I S N A S S Q L S S P P T S
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3361/1121 3391/1131 cca cag agt tet cca agg aaa gge tat act ttg get eee agt ggt act gtg gat aat ttt PQSSPRKGYTLAPSGTVDNF 3421/1141 3451/1151 tca gat tct ggt cac agt gaa att tct tca cga tcc agt att gtt agc aat tcg tct ttt SDSGHSEISSRSSIVSNSSF 3481/1161 3511/1171 gae tea gtg eea gte tea etg eac gat gag agg ege eag agg eat tet gte age ate gtg DSVPVSLHDEŘŘQŘHŠVSIV 3571/1191 gaa aca aac cta ggg atg ggc agg atg gag agg cgg acc atg att gaa cct gat cag tat ETNLGMGRMERRTMIEPDQY 3631/1211 age ttg ggg tcc tat gca cca atg tcc gag ggc cga ggc tta tat gct aca gta SLGSYAPMSEGRGLYATATV 3691/1231 att tet tet eca age aca gag gaa ett tee eag gat eag ggg gat ege geg tea ett gat ISSPSTEELSQDQGDRASLD 3751/1251 get get gae agt gge egt ggg age tgg aeg tea tge tea agt gge tee eat gat aat ata AADSGRGSWTSCSSGSHDNI 3781/1261 3811/1271 cag acg atc cag cac cag aga agc tgg gag act ctt cca ttc ggg cat act cac ttt gat QTIQHQRS WETLPFGHTHFD 3871/1291 tat tea ggg gat eet gea ggt tia tgg gea tea age age eat atg gae eaa att atg tit Y S G D P A G L W A S S S H M D Q I M F 3931/1311 tct gat cat agc aca aag tat aac agg caa aat caa agt aga gag agc ctt gaa caa gcc SDHSTKYNRQNQSRESLEQA 3991/1331 cag tee ega gea age tgg geg tet tee aca ggt tae tgg gga gaa gae tea gaa ggt gae Q S R A S W A S S T G Y W G E D S E G D 4051/1351 aca ggc aca ata aag cgg agg ggt gga aag gat gtt tcc att gaa gcc gaa agc agt agc T G T I K R R G G K D V S I E A E S S S 4111/1371 cta acg tct gtg act acg gaa gaa acc aag cct gtc ccc atg cct gcc cac ata gct gtg LTSVTTEETKPVPMPAHIAV 4171/1391 gca tca agt act aca aag ggg ctc att gca cga aag gag ggc agg tat cga gag ccc ccg ASSTTKGLIAKKEGKYKEPP 4231/1411 ccc acc cct ccc ggc tac att gga att ccc att act gac ttt cca gaa ggg cac tcc cat PTPPGYIGIPITDFPEGHSH 4291/1431 cca gcc agg aaa ccg ccg gac tac aac gtg gcc ctt cag aga tcg cgg atg gtc gca cga PARK PPDYNVAL QRSRMVAR 4321/1441 4351/1451 tcc tcc gac aca gct ggg cct tca tcc gta cag cag cca cat ggg cat ccc acc agc agc SSDTAGPSSVQQPHGHPTSS

PY motifs

agg cct gtg aac aaa cct cag tgg cat aaa ccg aac gag tct gac ccg cgc ctc gcc cct RPVNKPQWHKPNESDPRLAP BEPLACEMENT Sheet-Appln. 09/911,826 Filed July 20, 2001

4441/1481

4471/1491

tat cag tcc caa ggg ttt tcc acc gag gag gat gaa gat gaa caa gtt tct gct gtt tga
Y Q S Q G F S T E E D E D E Q V S A V \*

4501/1501

4531/1511

PDZ binding motif
ggc aca gac ttt tct gga agc aga gcc acc ctg aaa gga gag cac aag aag acg tcc
G T D F S G S R A S H L K G E H K K T S

4561/1521

4591/1531

tga gca ttg gag cct tgg aac tca cat tct gag gac ggt gga cca gtt tgc ctc ctt c

\* A L E P W N S H S E D G G P V C L L

(SEQ ID NO: 2)

Figure 3F

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## CDC25 Domain

hGRF4	SQISLLOLSTVEVA	TOLSMRNFELFRNIEPTEYIDDLFKLRSKTSCANLKRFEEVIN
dGRF4	SNVHFLHLNAYELA	IQLTLQDFANFRQIESTEYVDELFELRSRYGVPMLSKFAELVN
hEpac	SAEGLDLVSAKDI.A	GOLTDHDWSLFNSIHOVELIHYVLGPOHLRDVT-TANLERFMRRFN
mRasGRF2	KAECFETT.SAMELA	EQITLLDHIVFRSIPYEEFLGQGWMKLDKNERTPYIMKTSQHFN
dsos	DEITLITI.HPI.ELA	ROLTLLEFEHYKNVKPSELVGSPWTKKDKEVKSPNLLKIMKHTT
hRasGRP	VSLLEDHLEDERI SI	EHLTYLEFKSFRRISFSDYONYLVNSCVKENPTMERSIALCN
	: : : :::	
	• • • • • • • • • • • • • • • • • • • •	
hGRP4	OPTEWUACETT DEM	MAT VANVT TVARTAT TO CORRECT TO C
dGRF4	PPMFWMCETCARD	NOLKRMKIIKHFIKIALHCRECKNFNSMFAIISGLNLAPVARLRTT
hEpac	FI.OVERIATEI CT CD	NIVRRHKIVKQFIKIARHCKECRNFNSHFAIVSGLGHGAVSRLRQT
mRasGRF2	PMSNT.UXSOTMUNA	VPGPRAQLLRKFIKLAAHLKEQKNLNSFFAVMFGLSNSAISRLAHT
dSOS	MAMBRICACTURES	DISSRPNAIEKWVAVADICRCLHNYNGVLEITSALNRSPIYRLKKT
hRasGRP	GTSOWIOI WIT SHE	NYEERLAIHQRAIEVHUHVHLELNNFNGILSIVAAHGTASVYRLRWT
masora		TPQLRAEVFIKFIQVAQKLHQLQNFNTLMAVIGGLCHSSISRLKET
	: :	* • • • • • • • • • • • • • • •
hGRF4	WEET DURVERT FOR	ONI DRACANA TIMITA MANA
dGRF4	WPWI DERVOR END	LQDLFDPSRNMAKYRNVLNSQNL-QPPIIPLFPVIKKDLTFLHEGN
hEpac	WPDI DUPTIDET VCA	LODLHDPSRNMSKYROLVSAELLAQHPIIPFYPIVKKDLTFIHLGN
mRasGRF2	MENTERVANTISM	LERLLDPSWNHRVYR-LALAKLSPPVIPFNPLLLKDMTFIHEGN
dSOS	WWASVATVIWINT	LORTVSSEGRFKNLR-ETLKNCNPPAVPYLGMYLTDLAFIEEGT
hRasGRP	COMPUTATION OF	RELSDDHLKKYQERL-RSINPPCVPFFGRYLTNILHLEEGH
IIRasGRP		TELLSSSRNYDNYR-RAYGECTDFKIPILGVHLKDLISLYEAH
•	· · · ·	• • • • • • • • • • • • • • • • • • • •
hGRF4	DSKVDGLVNEERT	DATA PETRUICRUS CONTONES SALVERS
dGRF4	DTRVDGI.INFERI	LRMIAKEIRHVGRMASVNMDPALMFRTRKKKWRSLGSLSQGS
hEpac	HTT.VENI.INFERN	LRWLAREVRLLTHMCSSPYDLLSILELKGQSPSNALFSLNQMSASQ
mRasGRF2	PNFTFFG_I.VNFSFN	RMMARAARMLHECRSHNPVPLSPLRSRVSHLHEDSQVARISTCSE IRMISHIIREIRQFQQTAYRIDQQP
dsos	PDIJANTELTNESKE	REKVAEIIGEIQQYQNQPYCLNEES
hRasGRP	PDYLEDG-KVNVHKI	TALYNHISELVQLQEVAPPLEANKDL
	* *	· · · · · · · · · · · · · · · · · · ·
hGRF4	TNATVLDVAOTGG	HKKRVRRSSFLNAKKLYEDAQMARKVKQYLSNLELEMDEESLQ
dGRF4	SNAAAGTVIAANAGO	ATIKRRKKSTAAPNPKKMFEEAQMVRRVKAYLNSLKILSDEDLLH
hEpac		QSLSTRSPASTWAYVQQLKVIDNQRELS
mRasGRF2	**=*	KVIQYLLDKALVIDEDSLY
dsos		TIROFFEQLDPFNGLSDKOMSDYLY
hRasGRP		VHLLTLSLDLYYTEDEIY
		• •
hGRF4	TLSLOCEPATNT	(SEQ ID NO: 2)
dGRF4	RFSLECEPAHGS	(SEQ ID NO: 7)
hEpac	RLSRELEP	(SEQ ID NO:8)
mRasGRF2	ELSLKIEPRLPA	(SEQ ID NO: 9)
dsos	NESLRIEPRGCK	(SEQ ID NO: 10)
hRasGRP	ELSYAREPRNHR	(SEQ ID NO: 11)
	• ••	(000, 100, 11)



# GRF4-REM domain

Figure 5:

(SEQ ID NO: 13) (SEQ ID NO: 15) (SEQ ID NO: 14) (SEQ ID NO: 2) (SEQ ID NO: 12) -IKGGTVVKLIERLT-YHMYADPNF-VRTFLTYRSFCK-PQELLNLLIERFE VVKFASLNKLVEHLT-HDSKHDLQFLKTFLMTYQSFCT-PEKLMSKLQQRY--IRYASVEALLERLT-DLRFLSIDFLNTFLHTYRIFTT-ATVVLAKLSDIY--IRGGTKEALIEHLT-SHELVDAAFNVTMLITFRSILT-TREFFYALIYRY--IKG-TSERLTMHLVEEHSVVDPTFIEDFLLTYRTFLSSPMEVGKKLLEWFN RasGEF\_aimless\_ GRF2\_mouse\_ Sos\_mouse\_ CDC25



## Figure 7

## PDZ domain

13/34

LTKPSREAPLPFILLGGSEKGFGIFVDSVDSGSKATEAG-LKRGDQIL LTRSSRDEPLNFRIVGGYELRGVAIATGNAAVGIYISHVEPGSKAQDVG-LKRGDQIH NLKKDAKYGLGFQIIGGEKMGRLDLGIFISSVAPGGPADLDGCLKPGDRLI IVIHRGSTGLGFNIVGGEDGEGIFISFILAGGPADLSGELRKGDQIL VELPKTEEGLGFNIMGGKEQNSPIYISRIIPGGIADRHGGLKRGDQLL VKVQKGSEPLGISIVSGEKGGIYVSKVTVGSIAHQAG-LEYGDQLL  * : ::*	(SEQ ID NO: 2) (SEQ ID NO: 16) (SEQ ID NO: 17) (SEQ ID NO: 18) (SEQ ID NO: 19) (SEQ ID NO: 20)
LTKPSREAPLPFILLGGSEK LTRSSRDEPLNFRIVGGYELRGVAIA NLKKDAKYGLGFQIIGGEKMGRL IVIHRGSTGLGFNIVGGEDG VELPKTEEGLGFNIMGGKEQ VKVQKGSEPLGISIVSGEKG	EVNGONFENIOLSKAMEILR EVNGOSLDHVTSKRALEILT SVNSVSLEGVSHHAAIEILQ SVNGVDLRNASHEQAAIALK SVNGVSVEGEHHEKAVELLK EFNGINLRSATEQQARLIIG
hGRF4 dGRF4 hPTP-BAS-1 hPSD-95 rLin-7-C hDGL	hGRF4 dGRF4 hPTP-BAS-1 hPSD-95 rLin-7-C hDGL



## Figure 8

## MVFAVVERAGTIVLNDGEELDSWSVILNGSVEV---TYPDGKAEILCMGNSFGVSPTMDK LLFEPHSKAGTVLFSQGDKGTSWYIIWKGSVNVV--THGKGLVTTLHEGDDFGQLALVND AMFPVTHIAGETVIQQGNEGDNFYVVDQGEVDVY--VNGEWVTN-ISEGGSFGELALIYG MVFAVVDKAGTVVMSDGEELDSWSVLINGAVEI---EHANGSREELQMGDSFGILPTMDK CMYGRNYQQGSYIIKQGEPGNHIFVLAEGRLEV---FQGEKLLSSIPMWTTFGELAILYN RLRSVVYLPNDYVCKKGEIGREMYIIQAGQVQVLGGPDGKSVLVTLKAGSVFGEISLLAV

(SEQ ID NO: 21) (SEQ ID NO: 22) (SEQ ID NO: 23) (SEQ ID NO: 24) SEQ ID NO: 25) (SEQ ID NO: 2) --EYMKGVMRTKVDDCQFVCIAQQDYCRILNQVEKNMQKVEEE --LYHRGVMRTKCDDCQFVCITQTDYYRIQHQGEENTRRHEDE ---APRAATIILREDNCHFLRVDKQDFNRIIKDVEAKTMRLEEH --TPRAATVKAKTD-LKLWGIDRDSYRRILMGSTLRKRKMYEE ---CTRTASVKAITN-VKTWALDREVFQNIMRRTAQARDEQYRN GGGNRRTANVVAHGF-TNLFILDKKDLNEILVHYPESQKLLRKK PRKAR1B **hPKGII** dGRF4 **hEPAC** hGRF4 n-EAG

14/34

PRKAR1B

dGRF4 hEPAC

hGRF4

hPKGII

m-EAG

Replacement Sheet Appla. 09/911,826

# GRF4-RA domain

Figure 9:

REDFEIIRVFDGNNSYRSQISRNIVVAKHVSVQQVRDAALR HHRILDFSATPDLPDQVLRVFKADQQSRYIMISKDTTAKEVVIQAIR SILVTSQDKAPSVISRVLKKNNNRDSAVASEYELVQLLPGERELTIPASANVFYAMDGASH ; ; ; ;	RFHINDTPERYYIT-QVVGEVEEEILEDPVPLRNVKRPEGKRAQIFIR EFAVTATPDQYSLC-EVSVTPEGVIKQRRLPDQLSKLADRIQLSGR DFLLRHGEGPLLLHLASPVARLPQELLRVREEGAPFPGSRPQGGRLHGHCSEEEAPLAYR	YYD (SEQ ID NO: 26)  YYLKNNME (SEQ ID NO: 2)  SHGVHTRCG (SEQ ID NO: 27)
dgk-1a_ce_ GRF4 RalGDS_h_	dgk-1a_ce_ GRF4 RalGDS_h_	dgk-1a_ce_ GRF4 RalGDS_h_
	15/34	

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6568 bp

/translation="MKPLAIPANHGVMGQQEKHSLPADFTKLHLTDSLHPQVTHVSSS HSGCSITSDSGSSSLSDIYQATESEAGDMDLSGLPETAVDSEDDDDEEDIERASDPLM SRDIVRDCLEKDPIDRTDDDIEQLLEFMHQLPAFANMTMSVRRELCAVMVFAVVERAG TIVLNDGEELDSWSVILNGSVEVTYPDGKAEILCMGNSFGVSPTMDKEYMKGVMRTKV DDCQFVCIAQQDYCRILNQVEKNMQKVEEEGEIVMVKEHRELDRTGTRKGHIVIKGTS ERLTMHLVEEHSVVDPTFIEDFLLTYRTFLSSPMEVGKKLLEWFNDPSLRDKVTRVVL LWVNNHFNDFEGDPAMTRFLEEFENNLEREKMGGHLRLLNIACAAKAKRRLMTLTKPS REAPLPFILLGGSEKGFGIFVDSVDSGSKATEAGLKRGDQILEVNGQNFENIQLSKAM EILRNNTHLSITVKTNLFVFKELLTRLSEEKRNGAPHLPKIGDIKKASRYSIPDLAVD VEQVIGLEKVNKKSKANTVGGRNKLKKILDKTRISILPQKPYNDIGIGQSQDDSIVGL ROTKHIPTALPVSGTLSSSNPDLLQSHHRILDFSATPDLPDQVLRVFKADQQSRYIMI SKDTTAKEVVIQAIREFAVTATPDQYSLCEVSVTPEGVIKQRRLPDQLSKLADRIQLS GRYYLKNNMETETLCSDEDAQELLRESQISLLQLSTVEVATQLSMRNFELFRNIEPTE YIDDLFKLRSKTSCANLKRFEEVINQETFWVASEILRETNQLKRMKIIKHFIKIALHC RECKNFNSMFAIISGLNLAPVARLRTTWEKLPNKYEKLFQDLQDLFDPSRNMAKYRNV LNSQNLQPPIIPLFPVIKKDLTFLHEGNDSKVDGLVNFEKLRMIAKEIRHVGRMASVN MDPALMFRTRKKKWRSLGSLSQGSTNATVLDVAQTGGHKKRVRRSSFLNAKKLYEDAQ MARKVKQYLSNLELEMDEESLQTLSLQCEPATNTLPKNPGDKKPVKSETSPVAPRAGS QQKAQSLPQPQQQPPPAHKINQGLQVPAVSLYPSRKKVPVKDLPPFGINSPQALKKIL SLSEEGSLERHKKQAEDTISNASSQLSSPPTSPQSSPRKGYTLAPSGTVDNFSDSGHS EISSRSSIVSNSSFDSVPVSLHDERRQRHSVSIVETNLGMGRMERRTMIEPDQYSLGS YAPMSEGRGLYATATVISSPSTEELSQDQGDRASLDAADSGRGSWTSCSSGSHDNIQT IQHQRSWETLPFGHTHFDYSGDPAGLWASSSHMDQIMFSDHSTKYNRQNQSRESLEQA QSRASWASSTGYWGEDSEGDTGTIKRRGGKDVSIEAESSSLTSVTTEETKPVPMPAHI AVASSTTKGLIARKEGRYREPPPTPPGYIGIPITDFPEGHSHPARKPPDYNVALQRSR MVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKPNESDPRLAPYQSQGFSTEEDEDE QVSAV" [ SEQ ID NO: 2] 63. .4562

BASE COUNT 1974 a 1400 c 1463 g 1731 t ORIGIN

- 1 cttgccatcg tgagagattg gtacatgatg tgtaaattca gttcagcata tgtttcttca
- 61 ttatgaaacc actagcaatc ccagctaacc atggagttat gggccagcag gagaaacact
- 121 cactteetge agattteaca aaactgeate ttaetgacag tetecaceea caggtgacee
- 181 acgtttette tagecattea ggatgtagta teaetagtga ttetgggage ageagtettt
- 241 ctgatatcta ccaggccaca gaaagcgagg ctggtgatat ggacctgagt gggttgccag
- 301 aaacagcagt ggattccgaa gacgacgacg atgaagaaga cattgagaga gcatcagatc
- 361 ctctgatgag cagggacatt gtgagagact gcctagagaa ggacccaatt gaccggacag
- 421 atgatgacat tgaacaacte ttggaattta tgcaccagtt gcctgctttt gccaatatga
- 481 caatgtcagt gaggcgagaa ctctgtgctg tgatggtgtt cgcagtggtg gaaagagcag
- 541 ggaccatagt gttaaatgat ggtgaagagc tggactcctg gtcagtgatt ctcaatggat
- 601 ctgtggaagt gacttatcca gatggaaaag cagaaatact gtgcatggga aatagttttg
- 661 gtgtctctcc taccatggac aaagaataca tgaaaggagt gatgagaaca aaggtggatg
- 721 actgccagtt tgtctgcata gcccagcaag attactgccg tattctcaat caagtagaaa
- 781 agaacatgca aaaagttgaa gaggaaggag agattgttat ggtgaaagaa caccgagaac
- 841 ttgatcgaac tggaacaaga aagggacaca ttgtcatcaa gggtacctca gaaaggttaa
- 901 caatgcattt ggtggaagag cattcagtag tagatccaac attcatagaa gactttctgt
- 961 tgacctatag gactttictt tetageceaa tggaagtggg caaaaagtta ttggagtggt
- 1021 ttaatgaccc gagcctcagg gataaggtta cacgggtagt attattgtgg gtaaataatc
- 1081 acttcaatga ctttgaagga gatcctgcaa tgactcgatt tttagaagaa tttgaaaaca
- 1141 atctggaaag agagaaaatg ggtggacacc taaggctgtt gaatatcgcg tgtgctgcta
- 1201 aagcaaaaag aagattgatg acgttaacaa aaccatcccg agaagctcct ttgcctttta
- 1261 tettaetigg aggetetgag aagggattig gaatettigt tgacagtgta gatteaggta
- 1321 gcaaagcaac tgaagcaggc ttgaaacggg gggatcagat attagaagta aatggccaaa
- 1381 actttgaaaa cattcagctg tcaaaagcta tggaaattct tagaaataac acacatttat

Figure 19a

## REPLACEMENT Sheet . Apply 09/911,826 Filed July 20,2001



1441 ctatcactgt gaaaaccaat ttattigtat ttaaagaact tetaacaaga tigtcagaag 1501 agaaaagaaa tggtgccccc caccttccta aaattggtga cattaaaaag gccagtcgct 1561 actocattoc agatettget gtagatgtag aacaggtgat aggacttgaa aaagtgaaca 1621 aaaaaagtaa agccaacact gtgggaggaa ggaacaagct gaaaaagata ctcgacaaga 1681 ctcggatcag tatcttgcca cagaaaccat acaatgatat tgggattggt cagtctcaag 1741 atgacagcat agtaggatta aggcagacaa agcacatccc aactgcattg cctgtcagtg 1801 gaaccttate atecagtaat cetgatttat tgeagteaea teategeatt ttagaettea 1861 gtgctactcc tgacttgcca gatcaagtgc taagggtttt taaggctgat cagcaaagcc 1921 gctacatcat gatcagtaag gacactacag caaaggaagt ggtcattcag gctatcaggg 1981 agtttgetgt tactgecace eeggateaat atteactatg tgaggtetet gteacacetg 2041 agggagtaat caaacaaaga agacttccag atcagctttc caaacttgca gacagaatac 2101 aactgagtgg aaggtattat ctgaaaaaca acatggaaac agaaactctt tgttcagatg 2161 aagatgetea ggagttgttg agagagagte aaattteeet eetteagete ageaetgtgg 2221 aagttgcaac acagetetet atgegaaatt ttgaactett tegeaacatt gaacetaetg 2281 aatatataga tgatttattt aaactcagat caaaaaccag etgtgecaac etgaagagat 2341 ttgaagaagt cattaaccag gaaacatttt gggtagcatc tgaaattctc agagaaacaa 2401 accagetgaa gaggatgaag atcattaage attteateaa gatageaetg eaetgtaggg 2461 aatgeaagaa ttttaactea atgtttgeaa teateagtgg cetaaacetg geaceagtgg 2521 caagactgcg aacgacctgg gagaaacttc ccaataaata cgaaaaacta tttcaagatc 2581 tecaagacet gtttgateet tecagaaaca tggcaaaata tegtaatgtt etcaatagte 2641 aaaatetaca accteecata atecetetat teecagttat caaaaaggat eteacettee 2701 ttcacgaagg aaatgactca aaagtagacg ggctggtcaa ttttgagaag ctaaggatga 2761 ttgcaaaaga aattegteac gttggeegaa tggetteagt gaacatggae cetgeeetea 2821 tgttcaggac tcggaagaag aaatggcgga gtttggggtc tctcagccag ggtagtacaa 2881 atgcaacagt gctagatgtt gctcagacag gtggtcataa aaagcgggta cgtcgtagtt 2941 cettteteaa tgecaaaaag etttatgaag atgeceaaat ggetegaaaa gtgaageagt 3001 acctttccaa tttggageta gaaatggaeg aggagagtet teagacatta tetetgeagt 3061 gtgagccage aaccaacaca ttgcctaaga atcctggtga caaaaagcct gtcaaatccg 3121 agacetetee agtageteea agggeagggt cacaacagaa ageteagtee etgecacage 3181 cccagcagca gccaccacca gcacataaaa tcaaccaggg actacaggtt cccgccgtgt 3241 ccctttatcc ttcacggaag aaagtgcccg taaaggatct cccacctttt ggcataaact 3301 ctccacaage tttaaaaaaa attettett tgtetgaaga aggaagtttg gaaegteaca 3361 agaaacaggc tgaagataca atatcaaatg catcttegca getttettet cetectactt 3421 ctccacagag ttctccaagg aaaggctata ctttggctee cagtggtact gtggataatt 3481 tttcagattc tggtcacagt gaaattictt cacgatccag tattgttagc aattcgtctt 3541 ttgactcagt gccagtctca ctgcacgatg agaggcgcca gaggcattct gtcagcatcg 3601 tggaaacaaa cctagggatg ggcaggatgg agaggcggac catgattgaa cctgatcagt 3661 atagettggg gteetatgea ecaatgteeg agggeegagg ettatatget acagetacag 3721 taatttette teeaageaca gaggaacttt eecaggatea gggggatege gegteaettg 3781 atgetgetga cagtggeegt gggagetgga egteatgete aagtggetee catgataata 3841 tacagacgat ecageaceag agaagetggg agactettee attegggeat acteaetttg 3901 attattcagg ggatcctgca ggtttatggg catcaagcag ccatatggac caaattatgt 3961 tttctgatca tagcacaaag tataacaggc aaaatcaaag tagagagagc cttgaacaag 4021 cccagteceg ageaagetgg gegtetteca caggitactg gggagaagae teagaaggtg 4081 acacaggcac aataaagcgg aggggtggaa aggatgtttc cattgaagcc gaaagcagta 4141 gectaaegte tgtgactaeg gaagaaaeea ageetgteee eatgeetgee cacatagetg 4201 tggcatcaag tactacaaag gggctcattg cacgaaagga gggcaggtat cgagagccc 4261 egeceacece teceggetae attggaatte ceattactga etttecagaa gggeactece 4321 atccagccag gaaaccgccg gactacaacg tggcccttca gagatcgcgg atggtcgcac 4381 gatecteega cacagetggg cetteateeg tacageagee acatgggeat eccaceagea 4441 gcaggectgt gaacaaacct cagtggcata aaccgaacga gtctgacccg cgcctcgccc 4501 cttatcagtc ccaagggttt tccaccgagg aggatgaaga tgaacaagtt tctgctgttt

REPLACEMENT Sheet Appla 09/911,826 Filed July 20, 2001



4561 gaggcacaga citticigga agcagagcga gccaccigaa aggagagcac aagaagacgt 4621 cctgagcatt ggagccttgg aactcacatt ctgaggacgg tggaccagtt tgcctccttc 4681 congectiaa aageageatg gggettette teecettett cettteeest tigeatgtga 4741 aatactgtga agaaattgcc ctggcacttt tcagactttg ttgcttgaaa tgcacagtgc 4801 agcaatette gageteecae tgttgetgee tgecacatea cacagtatea ttecaaatte 4861 caagatcate acaacaagat gatteaetet ggetgeaett eteaatgeet ggaaggattt 4921 tttttaatet teettttaga ttteaateea gteetageae ttgateteat tgggataatg 4981 agaaaageta gecattgaac taettgggge etttaaceea eeaaggaaga caaagaaaaa 5041 caatgaaate etttgagtae agtgettgte eaettgttta caatgteete ettttaaaaa 5101 aaaaaatgag tttaaagatt ttgttcagag agtaaatata tatccattta atgattacag 5161 tattatttta aacettaagt agggttgeca geetggttte tgaaaaacca aatatgeegg 5221 acagggtgtg gccacaccaa gaagacggga agacctggct tgtgaccctg gcttcccatg 5281 teettetggt eteaecegeg aagtgeeeta teetggaagt atgaaatgtt agecaattaa 5341 taccaagaca ceteatetge teetteecca gtggatgggg ttettetgta aaactgtttg 5401 cacatggcca ggggagggaa ctaggaccct tgtgtcctgt ctgagcctta tggaggcagg 5461 acggigical tegeoggaigi giccigetee attgagatgg atggcaaace ceattittaa 5521 gitatattic titgattitt gitaattiag aggigtaggi titgittitt gittitigti 5581 tttttttaag agaaacattt ataactggat agcattgcag tgaaagcagc ttgggatgtt 5641 ggagetaatg ecagetgttt atactgetet tteaagaeag ecteeettta ttgaattgge 5701 attagggaat aaacaagcct ttaaacgtga taaaagatca aaaacctggt tagacatgcc 5761 agcetttgea aggeaggtta gteaceaaag actaacetee aagtggettt atggaegetg 5821 catatagaga aggeetaagt gtageaacea tetgeteaca getgetatta accetataat 5881 gactgaaatg accectecae tetattittg tgttgttttg cacagactee ggaaaagtga 5941 aggetgecaa tetgagtagt acteaaatgt gaggaactge tggtettgga tttttttee 6001 attaaattea getgateata ttgateagta gataaaegta aatagettea aattttaaaa 6061 gtggaattgc agtgttttt cactgtatca aacaatgtca gtgctttatt taataattct 6121 cttctgtatc atggcatttg tctacttgct tattacattg tcaattatgc atttgtaatt 6181 ttacatgtaa tatgcattat ttgccagttt tattatatag gctatggacc tcatgtgcat 6241 atagaaagac agaaatctag ctctaccaca agttgcacaa atgttatcta agcattaagt 6301 aattgtagaa cataggactg ctaatctcag ttcgctctgt gatgtcaagt gcagaatgta 6361 caattaactg gtgattteet catacttttg atactacttg tacctgtatg tettttagaa 6421 agacattggt ggagtetgta tecetttigt attittaata caataattgt acatattggt 6481 tatattttig tigaagatgg tagaaatgta ctatgtttat gettetacat ceagttigta 6541 caagetggaa aataaataaa tataacat [SEQ ID NO: 1]

Figure 19c



801 b.p.

1/1 31/11 ACT AAA GGG AAC AAA AGC TGG AGC TCC ACC GCG GTG GCG GCC GCT CTA GAA CTA GTG GAT T K G N K S W S S T A V A A A L E L V D L K G T K A G A P P R W R P L \* N \* W I R E Q K L E L H R G G G R S R T S G S 91/31 COC COE GGC TGC AGG AAT TICA AGG GGT GGG AAG GAT GTG TGC GGT GAG GGA GAG AGG AGG PPGCRNSSGGKDVSAEAESS PRAAGIQAVGRMSPLRQRAI A V G R M S P L R Q R A GLQEFKRWEGCLR 151/51 AGC ATG GTG CCC GTG ACT ACA GAG GAA GCC AAA CCT GTC CCT ATG CCT GCC CAC ATA GCT S H V P V T T E E A K P V P M P A H I A A W C P L Q R K P N L S L C L P T L L G A R D Y R G S Q T C P Y A C P H S 211/71 GTG ACG CCG AGC ACT ACC AAG GGA CTC ATC GCA CGG AAG GAA GGC AGG TAC CGG GAG CCG V T P S T T K G L I A R K E G R Y R E P
R R A L P R D S S H G R K A G T G S R
D A E H Y Q G T H R T E G R Q V P G A RQVPGAA 271/91 CCT CCC ACA CCT CCA GGC TAC GTG GGC ATC CCC ATT GCC GAT TTC CCA GAA GGG CCT TGC P P T P P G Y V G I P I A D F P E G P C L P H L Q A T W A S P L P I S Q K G L A S H T S R L R G H P H C R F P R R A L P 301/101 331/111 CAC COG GCC AGG AAG CCC CCG GAT TAC AAC GTG GCC CTG CAG CGG TCC CGC ATG GTG GCA H P A R K P P D Y N V A L Q R S R M V A
T R P G S P R I T T W P C S G P A W W H
P G Q E A P G L Q R G P A A V P H G G 391/131 COG CCC ACT GAG GCC CCG GCA CCG GGC CAG ACG CCG CCT GCA GCC GCA GCC AGC CGG CCG R P T E A P A P G Q T P P A A A A S R P G P L R P R H R A R R R L Q P Q P A G F • G P G T G P D A A C S R S Q P A G 421/141 451/151 GCC AGC AAG CCA CAG TGG CAC AAG CCC AGC GAC GCA GAC CCA CGC CTC GCG CCC TTC CAG G S K P Q W H K P S D A D P R L A P F A A S H S G T S P A T Q T H A S R P S QQATVAQAQRRRPTPRAL 481/161 511/171 CCC CAG GCT TCG CAG GAG CGG AGG AGG AGG AAG ATG AAC AAG TGT CTG CTG TTT GAG GCG P Q A S Q E R R R T K M N K C L L F E A R R L R R S G G R R \* T S V C C L R R A G F A G A E E D E D E Q V S A V \* G 571/191 CAG GCT CCT FGA TCC ACA GTG AGC CAC CCA AAG GAG AGC ACA AGA AGA CGT CCC AAG CCT Q A P \* S T V S H P K E S T R R R P K P R L L D P Q \* A T Q R R A Q E D V P S L G S L I H S E P P K G E H K K T S Q A I 601/201 631/211 TOG AGE CIT GGC ACG CAC ATC TGA GGA TGG TGG ACC AGT TTG CCT CCT TCC CTG CCT TAA W S L G T H I • G W W T S L P P S L P • G A L A R T S E D G G P V C L L P C L E P C L 691/231 AGC AGC ATG GGG CIT CIT CTC CCC TTC TTC CTT TCC CCT TTG CAT GTG AAA TAC TGT GAA S S M G L L L P F F L S P L H V K Y C E
A-A W G F F S P S S F P L C M \* N T V K
Q H G A S S P L L P F P F A C E I L \* F



FIGURE 19E

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